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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Vascular and Metabolic Implications of Novel Targeted Cancer Therapies

Focus on Kinase Inhibitors

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ABSTRACT

Novel targeted cancer therapies, especially kinase inhibitors, have revolutionized the treatment of many cancers and have dramatically improved the survival of several types of malignancies. Because kinases not only are important in cancer development and progression, but also play a critical role in the cardiovascular (CV) system and metabolic homeostasis, important CV and metabolic sequelae have been associated with several types of kinase inhibitors. This paper reviews the incidences and highlights potential mechanisms of vascular and metabolic perturbations associated with 3 classes of commonly used kinase inhibitors that target the vascular endothelial growth factor signaling pathway, the ABL kinase, and the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin signaling pathway. We propose preventive, screening, monitoring, and management strategies for CV care of patients treated with these novel agents.
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The past decade has been marked by a revolution in cancer therapy with the development of novel targeted therapies that have improved the prognosis of many cancer types. This progress has resulted, in part, from a new paradigm for cancer treatment with an evolution from relatively nonspecific cytotoxic agents to more selective, mechanism-based therapeutics. Unfortunately, adverse short- and long-term cardiovascular (CV) toxicities are important considerations with some of the novel therapies, prompting development of the new clinical field of cardio-oncology (also referred to as "onco-cardiology"). Although there has been much focus on the cardiomyopathic effects of cancer therapies, adverse vascular and metabolic sequelae of the novel cancer therapies have emerged as an important issue.

Tyrosine and serine/threonine kinases are important targets for cancer therapy, and these kinase inhibitors have become the fastest growing class of anticancer drugs (1). In general, kinase inhibitors are less toxic than older cancer therapies such as anthracyclines, alkylating agents, or ionizing radiation because they target cellular pathways that have been hijacked by the cancer cell. However, as kinases also play critical roles in the CV system, kinase inhibition can have adverse CV effects (2). Toxicities may be *on-target* where the intended target kinase

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also plays a critical role in CV system. In this case, such on-target toxicities may even serve as surrogates for antitumor response (3). On the other hand, most kinase inhibitors also inhibit kinases other than the cancer-promoting target, resulting in *off-target* toxicities.

Because many of the new kinase inhibitors target the vasculature or cancer metabolism, vascular and metabolic derangements have emerged as important issues in cardio-oncology. Moreover, multiple tyrosine kinase inhibitors (TKIs) are known to cause thyroid dysfunction, which can potentially complicate metabolic derangements (4). Coupled with the heterogeneity of both *on-* and *off-target* effects of specific agents, a wide spectrum of CV toxicities have been associated with these kinase inhibitors. This review will focus on the vascular and metabolic toxicities associated with 3 categories of kinase inhibitors commonly used in cancer therapy, categorized on the basis of their cellular targets: 1) kinase inhibitors targeting the vascular endothelial growth factor signaling pathway (VSP); 2) kinase inhibitors targeting ABL kinase; and 3) kinase inhibitors targeting the phosphoinositide 3-kinases (PI3Ks)/AKT/mammalian target of rapamycin (mTOR) signaling pathway.

KINASES AS TARGETS FOR CANCER THERAPY

Kinases are enzymes that transfer ≥1 phosphate group from adenosine triphosphate (ATP) to specific protein or lipid substrates. Kinase-directed modifications of these substrates control cell signaling, which regulates diverse cellular functions. Dysregulation of kinases can lead to a variety of pathologies, including malignancy. Indeed, most human cancers are associated with overactivation of kinases due to somatic point mutations, chromosomal rearrangements, or gene amplifications. There are approximately 20 lipid kinases and 518 protein kinases encoded by the human genome. On the basis of their substrate specificity, protein kinases can be further categorized into tyrosine kinases (TKs), serine/threonine kinases, and dual-specificity kinases. TKs are the most important targets for cancer drug development. For this reason, the majority of kinase inhibitors currently approved or in clinical trials are TKIs (5).

TKs can be classified as receptor tyrosine kinases (RTKs) and nonreceptor TKs. RTKs span the plasma membrane and are activated by binding of a ligand (most commonly a growth factor) to the extracellular domain, leading to dimerization of the receptor and activation of signaling. In contrast, nonreceptor TKs are located in the cytosol, the nucleus, or the inner surface of the plasma membrane and play an important role in relaying intracellular signals triggered by RTKs and other cell-surface receptors (**Central Illustration**) (6). To activate a substrate, kinases bind both the substrate and ATP, then transfer a phosphate group from ATP to the substrate, leading to substrate phosphorylation and activation.

Strategies to target kinases in cancer therapy include (**Central Illustration**):

1. Small molecule kinase inhibitors (TKIs): small molecules (molecular weight <1,000 Daltons) that interfere with binding of the kinase to ATP or substrates. Most current drugs targeting kinases belong to this category.
2. Monoclonal antibodies (mAbs) that bind the RTK or its ligand. As a result, they can be further subcategorized into mAbs directed against RTKs to prevent ligand binding (e.g., trastuzumab) or RTK dimerization and activation (e.g., pertuzumab); and mAbs directed against the circulating ligand to prevent it from binding to its receptor (e.g., bevacizumab).
3. Soluble decoy receptors ("ligand traps") bind the ligand, preventing it from binding to its receptor.

Small molecule inhibitors have been especially attractive for clinical use because they can be taken orally and can target more than 1 kinase, thus proving effective in several types of cancer.

CV ENDPOINTS IN ONCOLOGY TRIALS VERSUS CV TRIALS

As life expectancy increases, many diseases that predominantly affect older individuals will become more prevalent. Advancing age is a risk factor for CV disease, metabolic disorder, and cancer. Importantly, cancer and CV disease also share other common risk factors, such as tobacco use, obesity, and physical inactivity (7). As a result, cancer patients frequently have CV and metabolic comorbidities. Therefore, in the assessment of new cancer therapies, it becomes essential to distinguish between treatment-induced CV and metabolic adverse effects from treatment-independent events. A robust and consistent monitoring system with standard definitions for treatment-associated CV and metabolic adverse events is essential during the treatment course. In addition, to definitively determine whether a therapy causes CV disease, appropriate control groups are prerequisites.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CTCAE = Common Terminology Criteria for Adverse Events

CV = cardiovascular

mTOR = mammalian target of rapamycin

PI3K = phosphoinositide 3-kinase

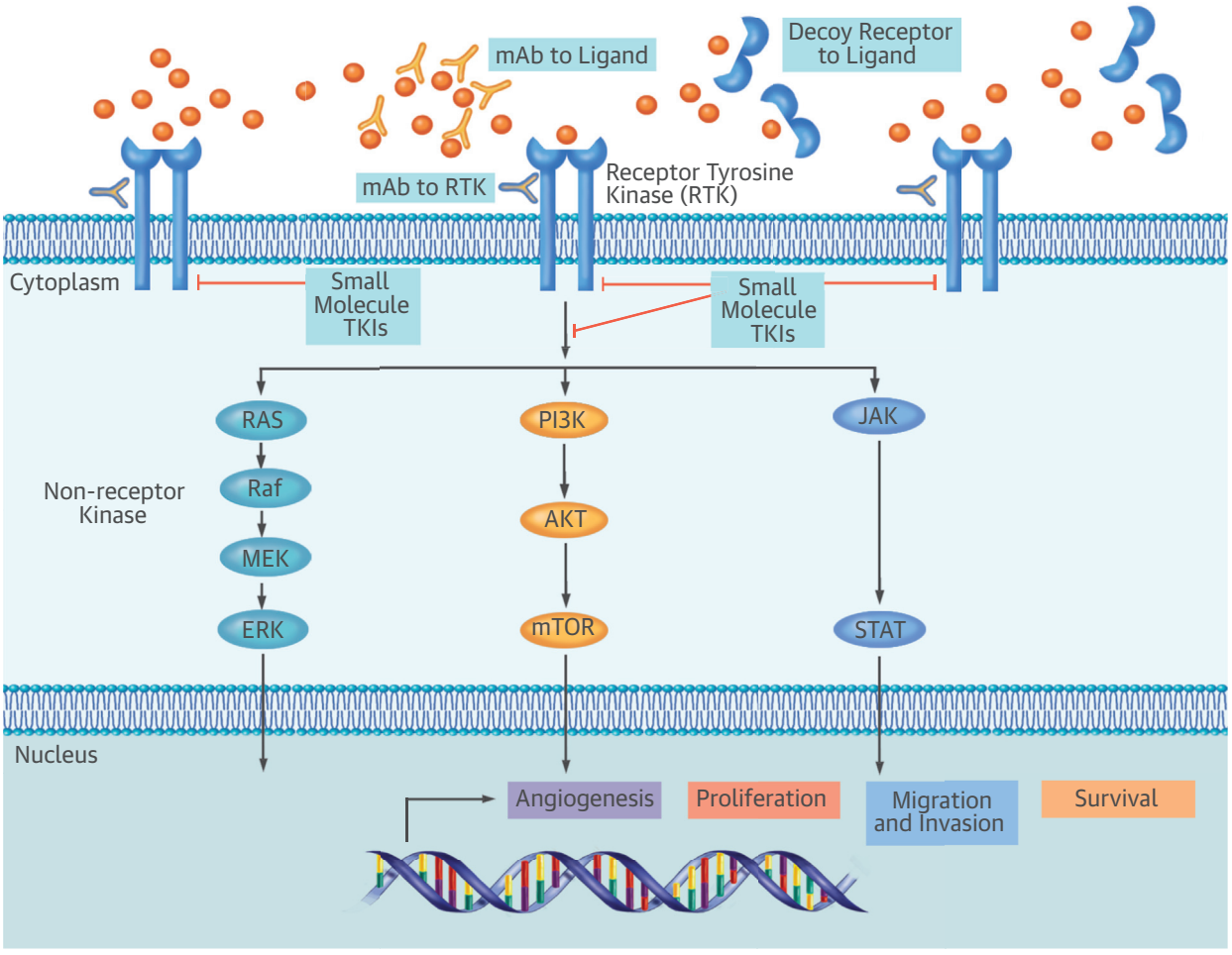
RTK = receptor tyrosine kinase

TKI = tyrosine kinase inhibitor

VEGF = vascular endothelial growth factor

VSP = vascular endothelial growth factor signaling pathway

CENTRAL ILLUSTRATION **Vascular and Metabolic Implications of Novel Targeted Cancer Therapies: Tyrosine Kinases as Targets for Cancer Treatment**



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Tyrosine kinases are divided into 2 main categories: receptor tyrosine kinases (RTKs) and non-RTKs. RTKs are activated upon binding of their respective ligands to their extracellular domain, leading to activation of various signaling pathways and promoting survival of tumor cells. Strategies to inhibit tyrosine kinases include: monoclonal antibodies (mAbs) targeting the ligand; soluble decoy receptors neutralizing the ligand; mAbs targeting the extracellular domain of RTKs and preventing RTK dimerization and activation; and small molecular tyrosine kinase inhibitors (TKIs) blocking intracellular signaling pathways. ERK = extracellular-signal-regulated kinase; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide-3 kinase.

Attempts to standardize CV endpoint definitions between CV trials of CV drugs and devices (e.g., criteria advanced by the various Academic Research Consortiums) and non-CV agents have been promulgated (e.g., Standardized Data Collection for Cardiovascular Trials Initiative), but have not been applied prospectively to date to the vast majority of novel anticancer agents. Instead, oncology clinical trials typically use a version of the Common Terminology Criteria for Adverse Events (CTCAE), a classification system developed by the National Cancer Institute to assess cancer therapy-related adverse events. The CTCAE categorizes events by severity using a 1 to 5 scale, with grade 5 being assigned to death and grade 1 to 2 typically indicating mild adverse events (8). In contrast, CV trials typically have focused the primary endpoint on major adverse CV events. There are major differences in reporting and grading of CV and metabolic adverse events in oncology trials compared with CV clinical trials, and these may limit detection of CV toxicities and reduce the ability to compare safety data among different cancer drugs (9) and

TABLE 1 CV Endpoints in Clinical Trials

CV Endpoint	Endpoint Definition Reference	Notes/Specific Endpoint Components
CV death	Standardized Data Collection for Cardiovascular Trials Initiative (10)	Includes death from AMI, sudden cardiac death, heart failure, stroke, CV procedures, CV hemorrhage
Myocardial infarction	Third Universal Definition of MI (101)	Caution in determining MI in setting of severe underlying illness such as end-stage cancer or infection, which may be associated with biomarker elevation (102)
Unstable angina	Standardized Data Collection for Cardiovascular Trials Initiative (10)	Hospitalization recommended as a requirement
TIA/stroke	Standardized Data Collection for Cardiovascular Trials Initiative (10)	Imaging studies, severity determination (modified Rankin scale); neurology participation in adjudication recommended; ischemic versus hemorrhagic
Revascularization PCI CABG	Standardized Data Collection for Cardiovascular Trials Initiative (10)	CABG and PCI; should be ischemia driven
Stent thrombosis	Academic Research Consortium (103)	Definite and probable stent thrombosis only
Peripheral arterial disease	TRA 2P-TIMI 50 (104)	Acute limb ischemia and peripheral revascularization

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CV = cardiovascular; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TRA 2P-TIMI 50 = Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis In Myocardial Infarction 50.

assess them in relation to a similar noncancer population. The need to standardize endpoints for CV endpoint trials of both CV and non-CV medications has also been recognized and codified by the Standardized Data Collection for Cardiovascular Trials Initiative (10). Experience with diabetes medications, which are mandated by the Food and Drug Administration (FDA) to be studied for CV safety, has demonstrated that large-scale trials can be conducted with standard definitions (11). In addition, large, multicenter CV trials invariably use central endpoint adjudication committees to ensure standardization of the endpoint process. One would hope that a similar approach would be adopted in cancer trials in the future, allowing for greater certainty in the CV assessment process. **Table 1** is a compilation of the main CV endpoints that should be included in such an approach and the basis for specific endpoint definitions.

All considerations of CV endpoints in oncology trials should be put in the context of specific cancer type, cancer prognosis, and the duration of therapy. For example, treatment of chronic myelogenous leukemia (CML) has been transformed by targeted kinase therapies, and patients may now have a near-normal life expectancy. In contrast, the cancer prognosis and duration of therapy are different for other cancer types, particularly solid tumors such as kidney and lung cancer. In this regard, communication between the cardiologist and oncologist is critical for individual optimization of patient care.

Much of the current data regarding toxicities derive from cancer clinical trials that excluded patients with a history of CV disease or history of vascular and metabolic disorders. Indeed, CV toxicities have the potential to be more frequent in a "real-world" population, where many patients may have marginally or even poorly controlled CV risk factors and underlying vascular disease. Post-approval FDA databases may help assess the CV safety of new cancer therapies in the general population.

HYPERTENSION MONITORING AND GRADING IN ONCOLOGY TRIALS

Older versions of CTCAE classifications for hypertension (HTN) had little similarity to standard cardiac definitions of HTN, such as those in the Joint National Committee 7/8 guidelines (**Table 2**). More recent versions of CTCAE classifications for HTN are more consistent with Joint National Committee 7/8 guidelines (12). Given this discrepancy, the incidence of HTN in older oncology trials initiated prior to 2009 might be under-reported.

PERIPHERAL ARTERIAL DISEASE AND OTHER VASCULAR TOXICITIES

Vascular events affecting the peripheral arteries are an important vascular toxicity associated with certain kinase inhibitors, but are generally not accurately reported in the oncology trials because CTCAE uses the vague term "peripheral ischemia" and captures vascular events as "a disorder characterized by impaired circulation to an extremity" (8). The majority of cancer therapy case series and studies discussed in this review used peripheral arterial occlusive disease interchangeably with peripheral arterial disease to characterize vascular toxicity. The term "peripheral arterial occlusive disease," which is increasingly used

TABLE 2 Comparison of CTCAE V3.0, V4.0, and JNC 7/8

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE version 3.0 (published in 2003)	Asymptomatic, transient (<24 h) increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously WNL; intervention not indicated	Recurrent or persistent (≥24 h) or symptomatic increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously WNL; monotherapy may be indicated	Requiring more than 1 drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
CTCAE version 4.0 (published in 2009)	Pre-hypertension (SBP 120–139 mm Hg or DBP 80–90 mm Hg)	Stage 1 HTN (SBP 140–159 mm Hg or DBP 90–99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated	Stage 2 HTN (SBP ≥160 mm Hg or DBP ≥100 mm Hg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
JNC 7/8	Normal BP: SBP <120 mm Hg; DBP <80 mm Hg Pre-hypertension: SBP 120–139 mm Hg; DBP 80–90 mm Hg; treatment required in high-risk cardiovascular patients Stage 1 HTN: SBP 140–159 mm Hg; DBP 90–99 mm Hg; treatment required Stage 2 HTN: SBP ≥160 mm Hg; DBP ≥100 mm Hg; treatment required				

BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; DBP = diastolic blood pressure; HTN = hypertension; JNC = Joint National Committee; SBP = systolic blood pressure; WNL = within normal limit.

by various oncology groups to characterize adverse vascular events, does not fully reflect adverse events that can occur in the cardiac and cerebral vasculature. However, this term gives very little insight into the specific pathophysiology (e.g., thrombosis vs. atherosclerosis) (9). To understand the incidence and severity of vascular toxicity in oncology studies, it will be useful to develop definitions for vascular events (VE) that match definitions commonly used in CV clinical trials (10). In this review, we will use VE to refer to both acute and chronic events related to the peripheral circulation reported in the published oncology data.

METABOLIC TOXICITIES

Hyperglycemia, hypertriglyceridemia, and hypercholesterolemia are listed as metabolic adverse effects in the current version of CTCAE (8). However, elevated low density lipoprotein (LDL), which is more relevant to adverse CV events, is not included.

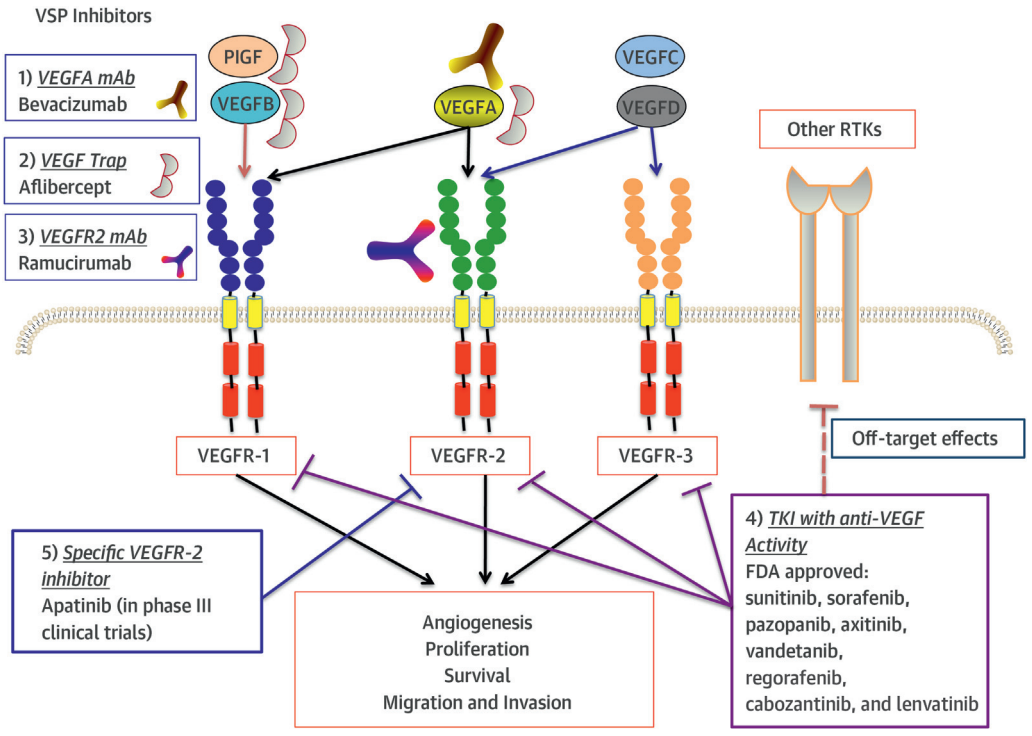
VSP INHIBITORS

VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALING IN TUMOR ANGIOGENESIS. Over a century ago, it was hypothesized that tumors secrete factors that promote the formation of new blood vessels (angiogenesis), ensuring the delivery of nutrients and oxygen for tumor growth (13). In 1971, Judah Folkman proposed targeting angiogenesis to treat human cancer (14). It took another 3 decades for the specific signaling pathways that promote angiogenesis to be elucidated. Hypoxia and low-nutrient environments, commonly found in the central region of solid tumors, lead to the stabilization of hypoxia inducible factor-1α, which in combination with its more stable partner, hypoxia inducible factor-1β, bind to cellular hypoxia-response elements that control angiogenesis. These include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other gene products that stimulate the development of new vasculature, allowing the tumor to grow and metastasize (15). In the past decade, agents that target tumor angiogenesis, and specifically VSP, have become effective cancer therapies.

The human VEGF family contains 5 glycoproteins: VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor (PIGF). All have a common VEGF homology domain. They bind to 3 RTKs: VEGFR-1 (FLT-1), VEGFR-2 (KDR/FLK-1), and VEGFR-3 (FLT-4), which are found primarily on the surface of vascular and lymphatic endothelial cells (ECs). Binding of the VEGF ligand to VEGF receptors leads to receptor activation and various cellular processes, including increased proliferation, survival, permeability, and migration (16). Although VEGFA binds to both VEGFR-1 and -2, VEGFR-2 serves as the main mediator of the mitogenic, angiogenic and permeability-enhancing effects and has, therefore, served as an important therapeutic target (17) (**Figure 1**).

The VEGF signaling pathway can generally be inhibited by 4 approaches: mAb directed against circulating VEGF, soluble decoy receptor "VEGF trap," antibodies directed against VEGFR, or small-molecule

FIGURE 1 VEGF Signaling and Inhibition Strategies



The mammalian VEGF family consists of 5 glycoproteins (VEGFA, VEGFB, VEGFC, VEGFD, and PIGF) that bind and activate 3 structurally similar receptor tyrosine kinases: VEGFR-1 (FLT-1), VEGFR-2 (KDR/FLK-1), and VEGFR-3 (FLT-4). VEGFA binds to both VEGFR-1 and -2; VEGFB and PIGF bind exclusively to VEGFR-1. VEGFR-3 is a specific receptor for VEGFC and VEGFD. Binding of VEGF to the VEGFR causes dimerization and autophosphorylation of the receptor, which activates downstream transduction pathways. VEGF-targeted approaches include: 1) mAbs targeting VEGFA; 2) a VEGF trap binding VEGFA, VEGFB, and PIGF; 3) an mAb targeting VEGFR-2; 4) small-molecule TKIs with anti-VEGF activity; and 5) specific VEGFR-2 inhibitors. FDA = Food and Drug Administration; mAb = monoclonal antibody; PIGF = placental growth factor; RTK = receptor tyrosine kinase; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VSP = vascular endothelial growth factor signaling pathway.

TKIs targeting VEGFR intracellularly (Figure 1). For example, bevacizumab (Avastin, Genentech, South San Francisco, California) is a fully humanized mAb that binds and neutralizes circulating VEGFA. In contrast, sunitinib and sorafenib are examples of small-molecule TKIs that target the VEGF and other receptors. Eight such small molecules (sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, and lenvatinib) have been approved by the FDA so far, while multiple other inhibitors are currently being tested in humans.

VSP INHIBITORS AND VASCULAR TOXICITIES. VSP inhibitors are associated with various CV toxicities including cardiomyopathy, HTN, arterial and/or venous thrombosis, and renal vascular injury. VSP inhibitor-associated cardiomyopathy was reviewed previously (18); here, we focus on the vascular and metabolic effects of these drugs.

HYPERTENSION. Incidence. HTN is the most common vascular toxicity associated with VSP inhibitors. The incidences of HTN are summarized in Table 3.

Nearly all patients treated with these agents experience a rise in their blood pressure (BP). In 1 study, 54 normotensive patients treated with sorafenib underwent 24-h ambulatory BP monitoring; 93% had a rise in BP by day 6, and most experienced a rise in BP in the first 24 h of therapy (19). HTN may also be dose-dependent and transient. In a study of home BP monitoring in patients receiving sunitinib, both systolic and diastolic BP had increased substantially by week 1 after initiation of sunitinib and decreased within 1 to 2 weeks after stopping therapy (20).

HTN as a biomarker for cancer response. Because HTN represents an on-target sequelae of VSP inhibitors,

TABLE 3 Incidences and RRs of HTN Associated With VSP Inhibitors

Agent	Molecular Targets	Study (Ref. #)	Overall Incidence of HTN (%)	High-Grade HTN (Grade 3 or 4) (%)	RR	
					All-Grade	High-Grade
Bevacizumab (mAb)	VEGFA	Meta-analysis, 12,656 patients, 20 trials (105)	23.6	7.9	3.02	5.28
Pazopanib (TKI)	VEGFR-1, VEGFR-3, PDGR-α, PDGFR-β, and c-KIT	Meta-analysis, 1,651 patients, 13 trials (106)	35.9	6.5	4.97	2.87
Sunitinib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, PDGR-α, PDGFR-β, FLT-3, and CSF-1R	Meta-analysis, 4,999 patients, 13 trials (107)	21.6	6.8	3.44	22.72
Sorafenib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, PDGR-α, PDGFR-β, FLT-3, RAF-1, and BRAF	Meta-analysis, 4,722 patients, 55 trials (108)	23.1	6.0	3.06	3.20
Axitinib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, PDGR-α, PDGFR-β, and CSF-1R	Meta-analysis, 1,908 patients, 10 trials (109)	40.1	13.1	3.00	1.71
Vandetanib (TKIs)	VEGFR-2, EGFR, and Ret	Meta-analysis, 3,154 patients, 11 trials (110)	24.2	6.4	5.1	8.06
Regorafenib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, TIE-2, PDGFR-β, FGFR-1, RET, KIT, and RAF	Meta-analysis, 1,069 patients, 5 trials (111)	44.4	12.5	3.76	8.39
Cabozantinib (TKI)	VEGFR-2, FLT-3, c-KIT, RET, and MET	Phase III clinical trial, 214 patients (112)	32.7	8.4	NA	NA
Aflibercept (VEGF trap)	VEGF	Meta-analysis, 4,451 patients, 15 trials (113)	42.4	17.4	4.47	4.97
Ramucirumab (VEGFR2 inhibitor)	VEGFR-2	Meta-analysis, 3,851 patients, 11 trials (114)	20.0	8.6	2.77	3.58
Lucitanib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, PDGR-α, PDGFR-β, FGFR-1, and FGFR-2	1 phase I/IIa study, 76 patients (115)	91	58	NA	NA
Lenvatinib (TKI)	VEGFR-1, VEGFR-2, VEGFR-3, FGFRs PDGFR-α, RET, and KIT	1 phase III trial, 261 patients (116)	69.3	42.9	NA	NA
Apatinib (TKI)	VEGFR-2	3 phase II trials (117–119)	39.1–64.4	8.51–36	NA	NA

CSF-1R = colony stimulating factor-1 receptor; FGFR = fibroblast growth factor receptor; mAb = monoclonal antibody; NA = not applicable; PDGFR = platelet-derived growth factor receptor; RR = risk ratio; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VSP = vascular endothelial growth factor signaling pathway.

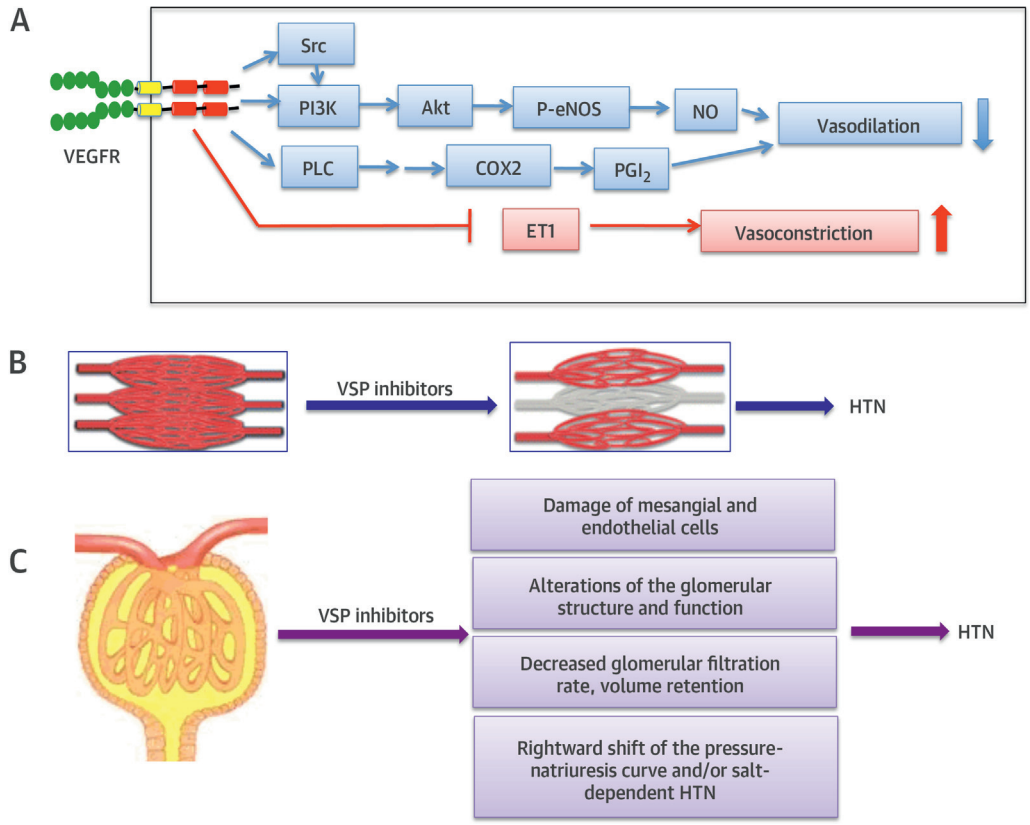
it may serve as a surrogate for cancer response. In 1 meta-analysis, bevacizumab-induced HTN correlated with tumor response in patients with metastatic colorectal cancer (21). HTN also correlated with a favorable outcome in other cancer types (22–24). However, these studies were retrospective analyses. In 1 small, prospective study of bevacizumab in 40 patients with recurrent glioblastoma, the development of HTN did not predict better outcomes (25). Large, prospective studies are needed to validate the role of HTN as a marker for cancer response and prognosis.

Relationship between proteinuria and HTN. Proteinuria is frequently observed in patients treated with VSP inhibitors and is often accompanied by HTN. In a recent meta-analysis including 6,882 patients with a variety of solid tumors treated with VSP inhibitors from 33 trials, the incidence of all-grade and high-grade proteinuria was 18.7% and 2.4%, respectively (26). Proteinuria is usually aggravated by concomitant HTN. In patients treated by bevacizumab, proteinuria was present in 54% of patients with grade 2/3 HTN and in only 16% of patients with grade 0/1 HTN (27). Patients with bevacizumab-induced proteinuria are also more commonly hypertensive (47.1% vs. 16.9%) (28). VEGF inhibition is likely a causal mechanism for both HTN and proteinuria, as demonstrated in other conditions, such as pre-eclampsia (see the following text).

Pathogenesis of VSP inhibitor-induced HTN. There have been several proposed mechanisms for VSP-inhibitor induced HTN. A combination of these diverse mechanisms is most likely to play a role in the pathogenesis of HTN.

Vasodilator and vasoconstrictor imbalance theory. VEGF induces nitric oxide (NO)-dependent arterial relaxation (29) and up-regulates NO production in human ECs via endothelial nitric oxide synthase phosphorylation and activation, thus playing an important role in maintaining baseline vascular tone (30). Conversely, bevacizumab decreases NO production in vitro (31). VEGF also leads to the production of another vasodilator, prostacyclin, and decreases endothelin-1 levels, a potent vasoconstrictor. Increased circulating levels of endothelin-1 after sunitinib therapy have been reported in parallel to a rise in BP in rodents, as well as in humans (32). Thus, the imbalance between vasodilators and vasoconstrictors

FIGURE 2 Proposed Mechanisms of VSP Inhibitor-Induced Hypertension



(A) VEGF in the circulation binds to VEGFRs expressed on endothelial cells and activates multiple downstream signaling pathways, including both Src and PI3K, resulting in activation of AKT kinase. AKT can directly phosphorylate and activate eNOS, leading to production of NO. VEGFR activation also activates PLC, which triggers a signaling cascade resulting in transcriptional activation of COX-2, leading to the production of the prostacyclin PGI_2. Both NO and PGI_2 are potent vasodilators. VEGFR activation also decreases production of ET-1 through unknown mechanisms. VSP inhibitors can lead to decreased production of NO and PGI_2, and increased production of ET-1, leading to HTN pathogenesis. **(B)** VEGF maintains capillary network integrity. When the VSP is inhibited, rarefaction (reduction of the density of capillary beds) can occur, which contributes to the development of HTN. **(C)** VEGF and the VEGFR are highly expressed in the kidneys, and VSP inhibitors can potentially alter glomerular structure and function and decrease the glomerular filtrate rate, leading to HTN pathogenesis. COX-2 = cyclooxygenease-2; eNOS = endothelial nitric oxide synthase; ET-1 = endothelin-1; HTN = hypertension; NO = nitric oxide; PGI_2 = prostacyclin; PI3K = phosphoinositide 3-kinase; PLC = phospholipase C; other abbreviations as in Figure 1.

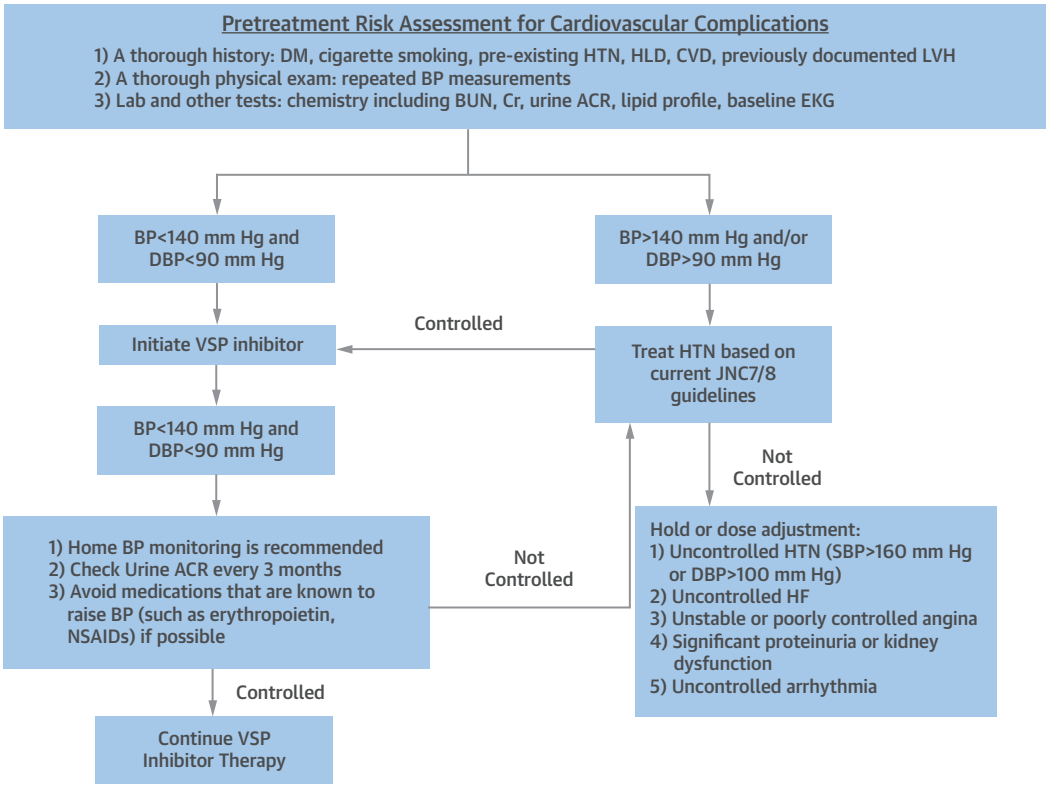
after VSP inhibition may be important in the development of HTN (Figure 2A).

Peripheral vascular resistance theory. VEGF is an important mediator for EC proliferation and survival. Chronic VEGF inhibition causes reduced EC survival, ultimately leading to a net reduction in tissue microvessel density and capillary rarefaction (loss of parallel capillary circulation) (33), which can increase afterload and contribute to HTN pathogenesis (Figure 2B).

Renal impairment theory. VEGF and VEGFR are highly expressed in the kidneys and play important roles in the proliferation, differentiation, and survival of mesangial cells and ECs (34). VSP inhibitors may alter glomerular structure and function, leading to a decreased glomerular filtration rate and HTN (Figure 2C).

"Pre-eclampsia-like" theory. Pre-eclampsia is characterized by HTN, proteinuria, and edema, and it affects up to 5% of pregnancies (35). Interestingly, this similar paradigm of "pre-eclampsia-like" syndrome has also been described in patients treated with VSP inhibitors (36). Several lines of evidence strongly implicate soluble fms-like tyrosine kinase receptor (sFlt-1), secreted by the placenta, as playing a causal role in the development of pre-eclampsia. sFlt-1, also called soluble VEGFR-1, binds to VEGF and PIGF, abrogating VEGF signaling, creating a condition

FIGURE 3 CV Risk Assessment and Monitoring During VSP Inhibitor Treatment



Cardiovascular (CV) risk factors should be carefully assessed before initiating VSP inhibitors. A thorough history and physical examination should be performed for each patient. Baseline creatinine to assess kidney function, urine ACR to assess proteinuria, lipid profile, and a baseline electrocardiogram to assess LVH are recommended. Pre-existing HTN needs to be treated and controlled before starting VSP inhibitors. Given the paucity of data, evidence-based recommendations cannot be made. ACEIs or ARBs are reasonable as first-line therapy for VSP inhibitor–induced HTN and proteinuria. ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin creatinine ratio; ARB = angiotensin II receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; Cr = creatinine; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; EKG = electrocardiogram; HTN = hypertension; JNC = Joint National Committee; LVH = left ventricular hypertrophy; SBP = systolic blood pressure; NSAID = nonsteroidal anti-inflammatory drug; VSP = vascular endothelial growth factor signaling pathway.

similar to that induced by VSP inhibitors (37). Renal biopsies in patients who develop "pre-eclampsia-like" syndrome, including HTN and proteinuria, after bevacizumab treatment showed features of thrombotic microangiopathy (TMA), similar to what is seen in severe pre-eclampsia (38). Given the infrequency of renal biopsies, the true rate of TMA with VSP inhibitors is unknown. In a recent French study, renal biopsies were done in 22 patients treated with various VSP inhibitors, and TMA was observed in 21 biopsy specimens (39), indicating that TMA might be more common than originally thought. How VEGF inhibition via sFlt-1 specifically leads to HTN in pre-eclampsia is an area of active investigation. Nevertheless, the similarities between pre-eclampsia and VSP inhibitor-induced HTN and proteinuria suggest similar underlying mechanisms.

Cardio-oncology considerations. There is no simple algorithm to follow in managing HTN induced by VSP inhibitors, and treatment needs to be individualized for each patient. The Cardiovascular Toxicities Panel of the National Cancer Institute published an expert opinion on management of VSP inhibitor-associated cardiac toxicity, including HTN, on the basis of consensus rather than on clinical outcome data (40). We proposed the following algorithm (**Figure 3**) (modified from de Jesus-Gonzalez et al. [12]).

ARTERIAL AND VENOUS THROMBOEMBOLISM. Incidence. Patients with malignancies have increased risks of thrombosis and hemorrhage. Numerous studies have shown that the thromboembolic events are further increased in cancer patients treated with VSP inhibitors. **Table 4** summaries the incidences of arterial

TABLE 4 Incidences and Risks of Arterial and Venous Thromboembolism Associated With VSP Inhibitors

Agent	Study (Ref. #)	Overall Incidence of VTE (%)	High-Grade VTE (Grade 3–5) (%)	RR of VTE		Study	Overall Incidence of ATE (%)	High-Grade ATE (Grade 3–5) (%)	RR of ATE	
				All-Grade	High-Grade				All-Grade	High-Grade
Bevacizumab (VEGF mAb)	Meta-analysis, 7,956 patients, 15 trials (120)	11.9	6.3	1.33	1.38	Meta-analysis, 12,617 patients, 20 trials (121)	3.3	2.0	1.44	2.14 (high-grade cardiac ischemia)
Pazopanib (TKI)	Meta-analysis, 7,441 patients, 17 trials (sunitinib: 3 trials; sorafenib: 4 trials; pazopanib: 3 trials; vandetanib: 5 trials; axitinib: 2 trials) (122)	2.76	1.92	1.10	0.85	Meta-analysis, 844 patients, 2 trials (123)	1.2	NA	4.61	NA
Sunitinib (TKI)						Meta-analysis, 4,628 patients, 4 trials (124)	1.3	NA	3.1	NA
Sorafenib (TKI)						Meta-analysis, 4,759 patients, 6 trials (124)	1.7	NA	2.39	NA
Axitinib (TKI)						Meta-analysis, 572 patients, 3 trials (123)	1.2	NA	1.17	NA
Vandetanib (TKIs)						Phase III RCT, 623 patients (123)	0	NA	0.13	NA
Regorafenib (TKI)	Phase III RCT in mCRC, 760 patients (125)	2	NA	NA	NA	NA	NA	NA	NA	NA
	Phase III RCT in advanced GIST, 199 patients (126)	No VTE or ATE events reported, but 1 patient in regorafenib arm died from cardiac arrest during treatment								
Cabozantinib (TKI)	Phase III RCT in MTC, 330 patients (112)	5.6	3.7	NA	NA	Phase III RCT in MTC (112)	2.3	0.9	NA	NA
Aflibercept (VEGF trap)	Phase III RCT in mCRC, 1,226 patients (127)	9.3	7.8	NA	NA	Phase III RCT in mCRC, 1,226 patients (127)	2.6	1.8	NA	NA
Ramucirumab (VEGFR2 mAb)	Phase III RCT in advanced gastric or GEJ adenocarcinoma, 665 patients (128)	3.98	2.45	NA	NA	Phase III RCT in advanced gastric or GEJ adenocarcinoma, 655 patients (128)	1.83	0.92	NA	NA
Lenvatinib (TKI)	Phase III trial, 261 patients (116)	5.4	3.8	NA	NA	Phase III trial, 261 patients (116)	5.4	2.7	NA	NA

ATE = arterial thromboembolic event; GEJ = gastroesophageal junction; mAb = monoclonal antibody; mCRC = metastatic colorectal cancer; MTC = medullary thyroid cancer; RCT = randomized controlled trial; TKI = tyrosine kinase inhibitor; VTE = venous thromboembolic event; other abbreviations as in Table 3.

and venous events in patients treated with these agents.

VSP inhibitors are associated with increased risks of both venous and arterial thromboembolic events; paradoxically, they are also associated with hemorrhagic events. One meta-analysis of 14,277 patients from 22 trials revealed that bevacizumab increases risks of high-grade bleeding in a dose-dependent manner (relative risk [RR]: 1.27 in low dose vs. 3.02 in high dose) (41). In a meta-analysis of 6,779 patients from 23 trials, the RR of all-grade bleeding events associated with sunitinib and sorafenib was 2.0 (95% CI: 1.14 to 3.49; p = 0.015) (42).

Mechanisms. ECs play a critical role in maintaining vascular homeostasis. They maintain normal blood vascular tone and viscosity, and prevent abnormal blood clotting and bleeding. VEGF signaling maintains EC integrity through activating survival and anti-apoptotic signaling (43). VEGF also increases the bioavailability of NO and prostacyclin, which, although best known as vasodilators, also have several vascular protective effects, including antiplatelet activities. Therefore, VEGF inhibition can alter the vascular hemostatic balance, interfere with the regenerative capacity of ECs, and cause defects of the endothelial layer that expose the underlying matrix, leading to both thrombosis and hemorrhage (44). An intriguing alternative hypothesis is that VSP inhibitors can form immune complexes that activate platelets and induce thrombosis (45,46).

Cardio-oncology considerations. Due to the presence of both thrombotic and hemorrhagic events, it is a clinical dilemma as to whether antiplatelets or anticoagulants should be used to prevent ATE or VTE

associated with VSP inhibitors. In a meta-analysis of 1,745 patients treated with bevacizumab, baseline or on-study aspirin use was associated with modest increases in grade 3 and 4 bleeding events, from 3.6% to 4.7% for bevacizumab-treated patients and from 1.7% to 2.2% for control subjects. The net clinical benefits of aspirin could not be assessed due to the small number of patients taking aspirin (47). Aspirin-based prophylaxis should be carefully considered for individual patients who are at high risk for ATEs. In a retrospective analysis of patients with metastatic colorectal cancer or advanced non-small cell lung cancer treated with bevacizumab and full-dose anticoagulation for VTE, bleeding complications were not significantly increased, suggesting that it may be safe to administer full-dose anticoagulation during bevacizumab treatment (48). Large, prospective clinical trials are needed to confirm whether anticoagulants can be given safely to patients on VSP inhibitors.

VSP INHIBITOR–RELATED HYPOGLYCEMIA. Emerging data suggest that some VSP inhibitors may affect glucose homeostasis. Sunitinib and sorafenib decrease blood glucose levels (49) and have been reported to induce cases of severe hypoglycemia (50,51). Further validation of sunitinib's glucose-lowing effect comes from studies showing that sunitinib therapy reduces the need for hyperglycemia treatment in patients with diabetes (52). The underlying mechanisms for VSP inhibitor-associated hypoglycemia remain unclear, but it may be an off-target effect, due to inhibition of PDGF signaling (53). Clinically, a diabetic regimen needs to be carefully reviewed and potentially modified in diabetic patients treated with these agents, and glucose levels should be closely monitored during treatment.

BCR-ABL INHIBITORS

Small-molecule TKIs have been most successful in treatment of CML. Imatinib was initially developed as a platelet-derived growth factor receptor (PDGFR) inhibitor, but was also found to inhibit other kinases, such as ABL and c-KIT (the stem cell factor receptor). In 2001, imatinib became the first small-molecule TKI approved by the FDA and has revolutionized the treatment of CML and other leukemias where the ABL TK is constitutively active.

Although imatinib has dramatically altered the natural history of CML, more than 30% of patients with CML will either be unable to tolerate or will develop resistance to imatinib. As a result, newer generations of BCR-ABL kinase inhibitors—dasatinib, nilotinib, bosutinib, and ponatinib—have been developed. Nilotinib is a close analog of imatinib with increased selectivity and approximately 20-fold higher potency against BCR-ABL (54). Dasatinib is a dual-specificity ABL- and SRC-family kinase inhibitor and is 100-fold more active against BCR-ABL in cell-based assays (55). Only ponatinib inhibits the "gatekeeper" T315I mutation, which is present in up to 20% of patients with resistance to other tyrosine kinase inhibitors (56).

Because the newer TKIs are more potent than imatinib, they are increasingly being used as front-line therapy for CML; nilotinib and dasatinib have FDA approval specifically for that indication. Whereas early data suggest that patients treated with newer agents achieve more rapid and deeper molecular response and have decreased progression to accelerated phase and blast crisis, this has not translated into better overall survival (57,58).

UNIQUE AND DIVERSE VASCULAR SAFETY PROFILES ASSOCIATED WITH BCR-ABL INHIBITORS. Vascular safety is an emerging challenge in patients treated with BCR-ABL inhibitors, especially the newer-generation agents. The various TKIs have distinct vascular safety profiles, most likely due to each compound's different kinase inhibition profiles and non-kinase targets.

Vascular safety of imatinib. Vascular toxicity is rare with imatinib treatment; in fact, on the basis of pre-clinical data and clinical observations, imatinib may actually have beneficial roles in the vasculature. Imatinib attenuates in-stent restenosis (59) and diabetes-associated atherosclerosis in a mouse model (60). Early clinical data suggests that imatinib lowers glucose levels in both diabetic and nondiabetic patients (49). Interestingly, in a large retrospective cohort analysis, patients with CML on imatinib treatment had lower rates of peripheral events compared with those treated initially with placebo (61). Such favorable effects also extend to the pulmonary vasculature, where pre-clinical data suggesting reversal of pulmonary arterial hypertension (PAH) has led to several clinical trials testing imatinib's potential role in the treatment of PAH (62).

Dasatinib-associated PAH and possible mechanisms. Despite the favorable vascular safety profile of imatinib, PAH can result from dasatinib. Recently, a French PAH registry reported a series of 9 dasatinib-associated PAH cases. All patients were diagnosed during treatment; the median time between initiation of dasatinib therapy and PAH diagnosis was 34 months (range 8 to 48 months) (63). At diagnosis, most patients had severe clinical, functional, and hemodynamic impairment with minimal acute vasodilator response, suggesting that isolated acute vasoconstriction may not represent the main mechanism

of dasatinib-induced PAH. The majority of patients failed to demonstrate complete hemodynamic recovery, and 2 died due to sudden death or cardiac failure at follow-up. Importantly, no PAH was reported in the context of other TKIs used for CML therapy in this registry.

It is difficult to estimate the incidence of dasatinib-associated PAH, because pulmonary pressures have not been systematically assessed in trials of dasatinib. The authors of the French registry estimated the lowest incidence of PAH in patients exposed to dasatinib to be 0.45%. In a Korean single-center study, 89 CML patients treated with dasatinib were followed for 6 years, and echocardiography was used to assess PAH. Patients with abnormal right ventricular systolic pressure or symptoms suggestive of PAH were evaluated with additional studies (such as catheterization) for a more definitive diagnosis. In the Korean series, 12.1% of patients developed PAH (64). The mechanism of dasatinib-associated PAH remains unclear.

Interestingly, dasatinib is associated with a higher incidence of pleural effusion, reported to range from 14% to 35% (65). The mechanisms underlying development of pleural effusion during dasatinib therapy are unclear, but are probably immune-mediated (66). When patients develop symptoms (i.e., chest pain, dyspnea, and dry cough) that can also occur in PAH, careful clinical examination and diagnostic tests are crucial in differential diagnosis.

Nilotinib-associated vascular toxicities and possible mechanisms. More recently, vascular toxicities have emerged as a critical concern with nilotinib (67–70). In a retrospective analysis of 179 patients who received nilotinib in 4 centers, 11 (6.15%) patients developed severe and previously unrecognized peripheral atherosclerosis that required invasive therapy, including angioplasty and limb amputation (67). In a 3-year follow-up of a pivotal trial comparing imatinib and nilotinib in newly diagnosed CML patients, 7 patients on nilotinib developed vascular events (VE), equating to a frequency of 1.2% after a median follow-up of 3 years, whereas there were no VE in the imatinib arm (71). After a follow-up of 4 years, 2 additional VE have occurred in the nilotinib arm (72).

Unfortunately, in most clinical trials with nilotinib, VE was not systematically evaluated or graded (58,73,74). A prospective study of 129 patients with CML systematically assessed ankle-brachial index in all patients. Peripheral arterial disease was discovered in 6.3% with first-line imatinib, 26% with first-line nilotinib, and 35.7% with second-line nilotinib—far higher than previously reported (72), suggesting the possibility that accelerated atherosclerosis may be the underlying cause of nilotinib-associated vascular events. Indeed, several clinical studies suggest that nilotinib is associated with elevations in glucose (71), total cholesterol, and LDL (72), which are risk factors for developing atherosclerosis. A more in-depth study of glucose metabolism in 10 CML patients receiving nilotinib demonstrated insulin resistance and compensatory hyperinsulinemia (75). Nilotinib treatment is also associated with hypothyroidism, which can affect lipid and glucose metabolism (76). Therefore, an accelerated metabolic dysregulation may be involved in the formation of atherosclerotic plaques and pathogenesis of vascular atherosclerosis.

Ponatinib-associated vascular toxicities and possible mechanisms. Ponatinib was initially approved via the FDA's expedited program for drug approval after encouraging results from a phase 2 study of 449 patients who had failed other TKIs (56). With a median follow-up of 12.8 months, the reported CV, cerebrovascular, and peripheral VEs were 2.2%, 0.7%, and 1.6%, respectively (77). These numbers were deemed as not concerning given ponatinib's anticancer potency. Subsequent follow-up confirmed ponatinib as highly effective in CML patients who had become resistant to other TKIs; for these patients, the only other treatment option would be a stem cell transplant, which would portend significant morbidity. However, over a median follow-up of 27.9 months, serious "arterial thrombotic events" occurred in 19% of ponatinib-treated patients, including CV events (10%), cerebrovascular events (7%), and peripheral VEs (7%), with some patients having more than 1 event. In addition, 5% patients experienced VTE (78). At least 5 patients died from VEs thought to be due to ponatinib. Because of the severe vascular complications detected during an interval analysis of the trial at 24 months, sale of ponatinib in the United States was temporarily suspended in October 2013. However, after further assessment of the data and consideration of the lack of other effective treatments available for T315I mutant CML, sale of ponatinib resumed in January 2014 under narrower indications for treatment and a black box warning about increased risk of arterial and venous occlusive events (79). Retrospective analysis of the phase III trial suggests older age (≥65 years, RR: 1.8), history of ischemic disease (RR: 2.6), diabetes (RR: 2.5), and HTN (RR: 3.2) as risk factors associated with serious arterial thrombotic events during ponatinib treatment (78).

The underlying mechanisms of ponatinib-induced VE are largely unknown. In a recent study, ponatinib blocked platelet immune-receptor tyrosine-based

activation motif signaling, as well as platelet spreading, aggregation, and aggregate formation. Thus, ponatinib serves as a platelet antagonist, suggesting that the VEs are not due to platelet activation (80). Vascular toxicities may also represent off-target side effects. Ponatinib inhibits numerous other TKs, including SRC, FGFR, PDGFR, and VEGFR1-3, which are important kinases in the vasculature (81). The potency of ponatinib inhibition against VEGFR-2 is similar to the VSP inhibitors sunitinib and sorafenib (82), thus explaining the high incidence of HTN (26%) in patients treated with ponatinib (78). It remains to be seen how much of the vascular events associated with ponatinib are due to these off-target kinase inhibitions, specifically VEGFR-2. The use of lower doses of ponatinib (i.e., a starting dose of 15 or 30 mg, rather than the FDA-approved dose of 45 mg) is also being explored in a randomized trial, in which vascular safety will be carefully assessed (NCT02398825).

CARDIO-ONCOLOGY CONSIDERATIONS. BCL-ABL kinase inhibitors have transformed the prognosis of CML, and as a result, many patients taking TKIs for CML will be on therapy for 10 years or longer. The 4-year overall survival rate for CML patients is as high as 95% (83), and survival rates of CML patients who experience a complete cytogenetic response is comparable to their age-matched control subjects (84). Therefore, it is essential for physicians to prevent and manage acute and chronic CV complications associated with these agents.

Patients taking TKIs for CML, especially agents other than imatinib, need to be carefully counseled about management of modifiable risk factors for cardiac and vascular events (**Figure 4**). In addition, some investigators have proposed specific screening tools when considering TKI therapy. For instance, it has been proposed that patients starting dasatinib should be routinely screened for PAH by echocardiography, although this is not yet a standard practice (63). A validated score system, such as the European Society of Cardiology score, could be used to determine the individual risk of vascular events before prescribing nilotinib or ponatinib. Given the high frequency of VEs associated with nilotinib, it should probably not be prescribed as front line therapy for patients with multiple risk factors for vascular disease (e.g., smoking, HTN, diabetes, hypercholesterolemia) if other agents are available (85). Because ponatinib-induced vascular toxicity can be severe, and sometimes fatal, until further data are available, ponatinib should only be considered in patients who either have the T315I mutation or have not tolerated or not responded to other TKIs, and CV risk factors need to be tightly controlled and optimized when the drug is started. It is unclear whether antiplatelet agents or anticoagulants should be routinely used in conjunction with ponatinib, and although some clinicians have initiated this practice, the risk of bleeding from cytopenias or thrombocytosis needs to be considered. We do suggest a low threshold for involvement of cardiologists in the care of CML patients being treated with second-line therapies, especially nilotinib or ponatinib.

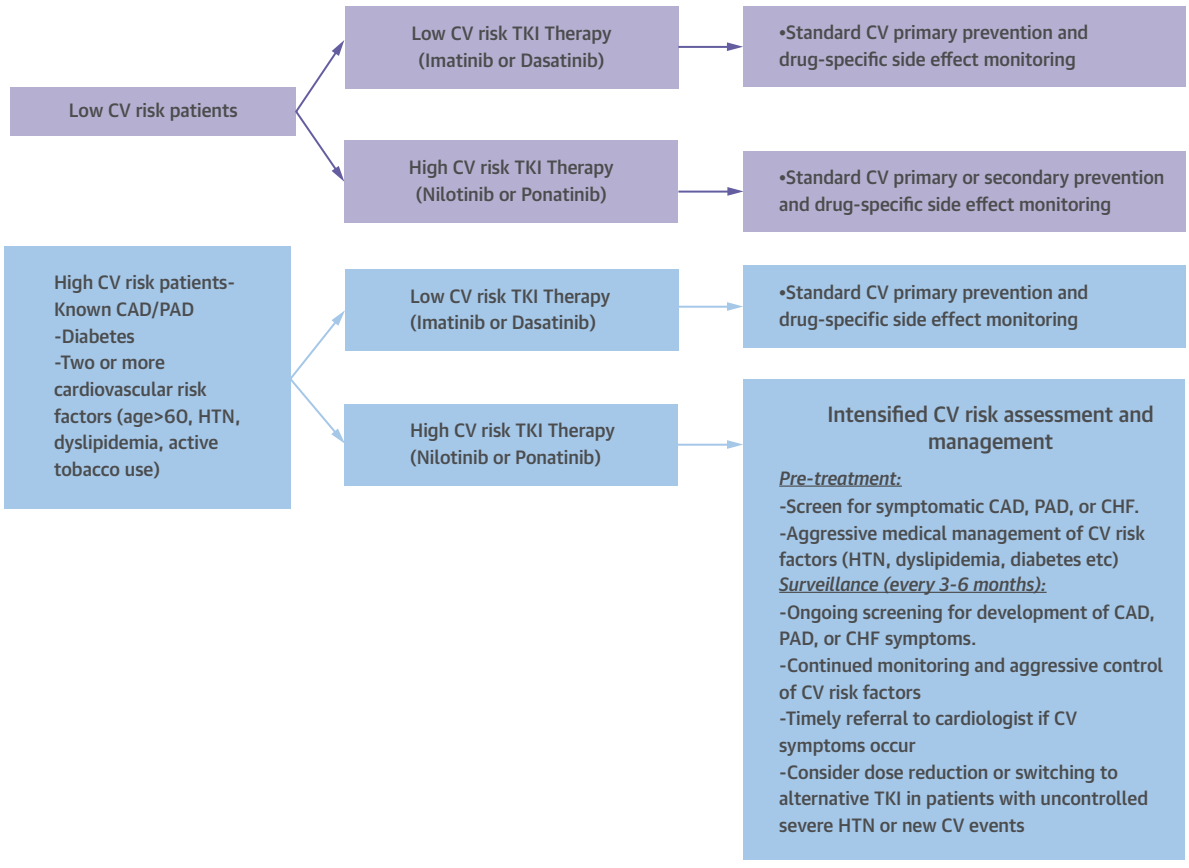
PI3K/AKT/mTOR INHIBITORS

PI3Ks are lipid kinases that are major downstream effectors of RTKs and G-protein-coupled receptors (GPCRs) and regulate diverse cellular processes by activating downstream mediators, such as the serine/threonine kinases AKT and mTOR (**Figure 5**). The PI3K/AKT/mTOR signaling cascade is 1 of the most important intracellular pathways and is frequently mutated in cancers (86). PI3Ks can be divided into 3 classes (I, II, III) on the basis of their structural characteristics and substrate and tissue specificity. Class I PI3Ks are the best characterized and are subdivided into Class IA and IB. Class IA PI3K (consisting of a p85 regulatory subunit and a p110 catalytic subunit: p110α, p110β, or p110δ) is activated by both RTKs and GPCRs, whereas class IB PI3K (consisting of a p101 regulatory subunit and a p110γ catalytic subunit) is activated by GPCRs (87).

Drugs targeting the PI3K/AKT/mTOR pathway have emerged as important cancer therapies. Currently, 1 p110δ-specific inhibitor (idelalisib) and 2 mTORC1 inhibitors (everolimus and temsirolimus) have been granted FDA approval. Additionally, a multitude of pan-PI3K inhibitors, p110α-specific inhibitors, dual PI3K/mTOR inhibitors, AKT inhibitors, and dual mTORC1/mTORC2 inhibitors are in clinical trials (**Figure 5**), either as single agents or in combination with other agents.

CARDIAC AND METABOLIC CONSIDERATIONS DURING THE ONGOING CLINICAL TRIALS TARGETING PI3K/AKT/MTOR. PI3K/AKT/mTOR also plays critical roles in the CV system. Insulin and insulin growth factor are potent activators of PI3K/AKT/mTOR signaling in cardiac myocytes and have been implicated in cardiac hypertrophy and protection of myocytes from apoptosis (88). Among the class I PI3Ks expressed in the heart, p110α and p110γ are more highly expressed than p110β and p110δ (89). The roles of different PI3K isoforms in the CV system have not been extensively evaluated, but evidence from transgenic and knockout mice studies indicates that different isoforms may have distinct effects. In a

FIGURE 4 **Proposed CV Risk Assessment and Management in CML Patients Receiving TKI Treatment**

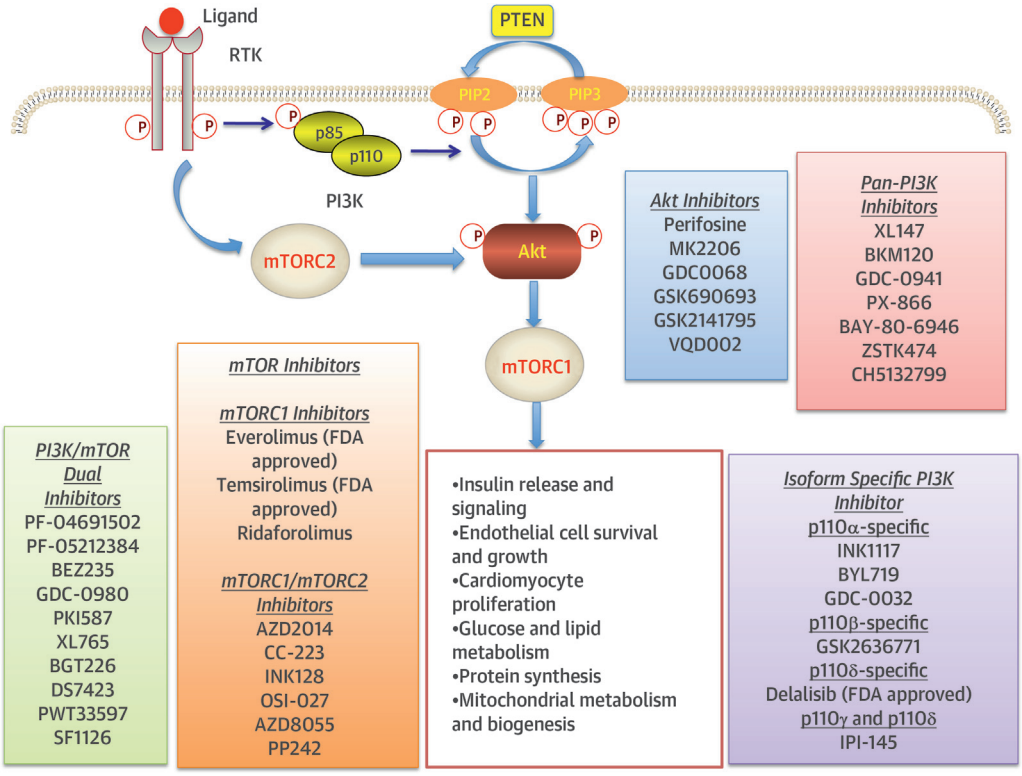


CAD = coronary artery disease; CHF = congestive heart failure; CML = chronic myelogenous leukemia; CV = cardiovascular; HTN = hypertension; PAD = peripheral arterial disease; TKI = tyrosine kinase inhibitor.

cardiac-specific transgenic mouse model expressing a constitutively active PI3K (p110α) mutant, heart size was significantly increased due to cardiac hypertrophy, but the cardiac function and lifespan were normal. In contrast, in a cardiac-specific mouse model expressing a dominant negative PI3K (p110α) mutant, the heart was significantly smaller. Under basal conditions, cardiac function in these mice was not compromised. However, in the presence of pathologic stimuli, cardiac function and lifespan were significantly decreased (90), indicating the importance of p110α in maintaining cardiac structure and function in pathological settings of stress. This raises concern that the p110α-specific and pan-PI3K inhibitors may cause cardiac dysfunction. However, PI3K (p110γ), which is linked to GPCRs, is critical for the induction of myocardial hypertrophy, interstitial fibrosis, and cardiac dysfunction in response to β-adrenergic receptor stimulation in vivo. PI3K (p110γ) knockout mice are actually protected against isoproterenol-induced heart failure, suggesting that PI3K (p110γ) mediates pathological cardiac hypertrophy (91). AKT and mTOR are also involved in cardiac hypertrophy and survival. Recent evidence suggests that activation of this pathway is likely to counteract fibrosis and cell death, thus preserving cardiac function (88). This suggests that inhibiting AKT or mTOR might result in deterioration of cardiac function in patients with baseline cardiac hypertrophy (92). Thus, given the complexity of the PI3K/AKT/mTOR pathway in the CV system, close monitoring of cardiac function is warranted during ongoing clinical trials of these novel agents.

The PI3K/AKT/mTOR pathway can modulate the insulin-signaling pathway (93). PI3K knockout mice display hyperinsulinemia, insulin resistance, and glucose intolerance (94). In a mouse model of type 2 diabetes, mTOR inhibition increased insulin

FIGURE 5 PI3K/AKT/mTOR Signaling Pathway and Inhibition Strategies



Many novel agents targeting this signaling pathway are under clinical development. mTORC = mammalian target of rapamycin complex; RTK = receptor tyrosine kinase; other abbreviations as in Figures 1 and 2.

resistance and reduced beta cell function and mass (95). In rat adipose cells, PI3K and mTOR inhibitors impaired the insulin-signaling pathway regulating lipoprotein lipase (LPL) (96).

METABOLIC TOXICITIES ASSOCIATED WITH PI3K/AKT/MTOR INHIBITORS. Due to the important role of PI3K/AKT/mTOR signaling in glucose and lipid metabolism, targeting this pathway for cancer treatment would be predicted to cause a spectrum of metabolic derangements, including hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. For this reason, patients with diabetes and ischemic heart disease were often excluded from clinical trials (97); data on the specific incidence and spectrum of metabolic toxicities during treatment with PI3K/AKT/mTOR pathway inhibitors are therefore incomplete. Still, a high incidence of unfavorable metabolic adverse effects was observed to be associated with these agents. In a phase III trial evaluating everolimus in metastatic renal cell carcinoma (mRCC), the incidences of hypertriglyceridemia, hypercholesterolemia, and hyperglycemia were 71%, 76%, and 50%, respectively, which were significantly higher than placebo (30%, 32%, and 23%, respectively) (97). Similar findings were reported in a clinical trial using temsirolimus in advanced renal cell carcinoma (98). The most common laboratory abnormalities associated with idelalisib are hyperglycemia and hypertriglyceridemia, which occurred in 54% and 56% of patients, respectively (99). The frequency of elevation in LDL, an important atherogenic component of cholesterol, is not known because it is not 1 of the adverse events listed in the CTCAE and is not often reported in oncology trials (100).

CARDIO-ONCOLOGY CONSIDERATIONS. Owing to the significant effect of mTOR inhibitors on lipid and glucose metabolism, the Task Force of National Cancer Institute Investigational Drug Steering Committee has proposed specific management of the metabolic side effects of these agents (**Table 5**) (100). Because idelalisib was just approved by the FDA in 2014, clinical experience regarding the incidence of

TABLE 5 Summary of Glycemic and Lipid Thresholds for Eligibility, Goals, Dose-Limiting Toxicity, and Management

	Glucose	Lipid
Eligibility for trials	Fasting glucose <160 mg/dl	LDL <190 mg/dl Triglycerides <300 mg/dl
Goals on trials	HbA1C ≤8% Fasting glucose <160 mg/dl Random glucose <200 mg/dl	LDL <190 mg/dl if no CV risk factors; LDL <100 mg/dl if high risk; Triglycerides <300 mg/dl
Dose-limiting toxicity	Grade 3 or asymptomatic grade 4 hyperglycemia not improving despite appropriate treatment for 1 week Symptomatic grade 4 hyperglycemia (>500 mg/dl)	Grade 3 to 4 hyperlipidemia (total cholesterol >400 mg/dl or triglycerides >500 mg/dl) not improving despite appropriate treatment for 4 weeks
Management	Grade 2 hyperglycemia (161–250 mg/dl): lifestyle modification, metformin; if not controlled, add sulfonylurea; if still not controlled, add basal insulin Asymptomatic grade 3 hyperglycemia (250–500 mg/dl): begin metformin and sulfonylurea; if not controlled, add basal insulin; if not controlled, stop oral agents, add pre-meal insulin Symptomatic stage 3 hyperglycemia (250–500 mg/dl) or grade 4 hyperglycemia (>500 mg/dl): baseline insulin, pre-meal insulin, and diabetes consultation	Triglycerides 150–299 mg/dl: lifestyle modification, treat LDL to target Triglycerides 300–499 mg/dl: lifestyle modification, treat LDL to target, consider drug therapy, especially if high CV risk Triglyceride ≥500 mg/dl: lifestyle modification + drug therapy (fibrate, omega-3 acid, extended-release niacin) Elevated LDL should be treated with statins if lifestyle modification fails

Modified from Busaidy et al. (100).
CV = cardiovascular; HbA1C = glycated hemoglobin; LDL = low-density lipoprotein.

metabolic toxicities, their clinical effect, and management is lacking.

SUMMARY AND FUTURE DIRECTIONS

Kinase inhibitors are important anticancer agents and have improved oncological outcomes. Novel agents in development hold considerable promise. However, CV and metabolic adverse events need to be considered and carefully managed when treating patients with these agents. Further insights into the mechanism underlying these adverse events may allow design of more narrowly targeted agents with fewer off-target effects. In the meantime, CV specialists and oncologists need to work closely to better define cardiac, vascular, and metabolic perturbations that can affect cancer patients during anticancer treatment and survivorship.

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